We Claim:

1. A pharmaceutical composition comprising a pharmaceutically effective amount of an insulin sensitizer agent and a pharmaceutically effective amount of an FBPase inhibitor, or prodrugs or salts thereof.

2. The pharmaceutical composition of claim 1 wherein said insulin sensitizer is a thiazolidinedione.

3. The pharmaceutical composition of claim 2 wherein said thiazolidinedione is selected from the group consisting of BRL 49653, troglitazone, pioglitazone, ciglitazone, WAY-120,744, englitazone, AD 5075, Gl-262570, SB219994, SB219993, and darglitazone.

4. The pharmaceutical composition of claim 1 wherein said insulin sensitizer is a PPAR γ agonist.

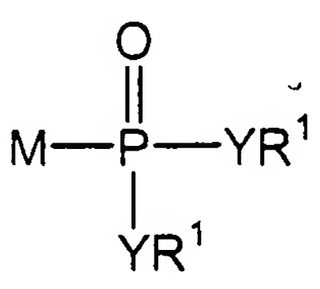
5. The pharmaceutical composition of claim 4 wherein said PPAR γ agonist is selected from the group consisting of BRL 49653, troglitazone, pioglitazone, ciglitazone, WAY-120,744, englitazone, AD 5075, darglitazone, Gl-262570, SB 217092, SB 236636, SB 217092, SB 219994, and SB 219993.

6. The pharmaceutical composition of claim 1 wherein said insulin sensitizer is a RXR ligand.

7. The pharmaceutical composition of claim 6 wherein said RXR ligand is selected from the group consisting of 9-cis retinoic acid, LG 100268 and LG 1069.

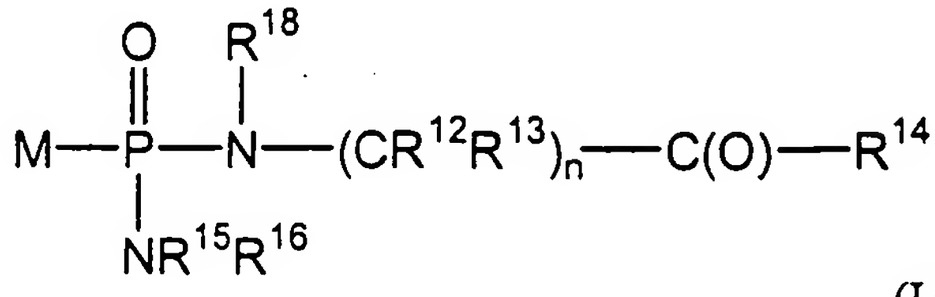
8. The pharmaceutical composition of claim 1 wherein said insulin sensitizer is selected from the group consisting of an angiotensin converting enzyme inhibitor, a renin inhibitor, and an angiotensin antagonist.

9. The pharmaceutical composition of claim 1 wherein said FBPase inhibitor is a compound selected from the group consisting of formulae I and IA:



(I)

and



(IA)

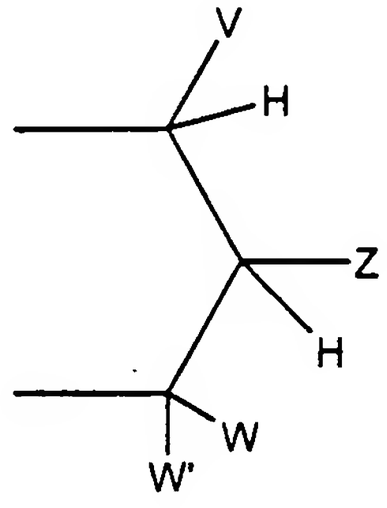
wherein *in vivo* or *in vitro* compounds of formulae I and IA are converted to $M\text{-}PO_3^{2-}$ which inhibits FBPase and wherein

Y is independently selected from the group consisting of -O-, and $-NR^6-$;

when Y is -O-, then R^1 attached to -O- is independently selected from the group consisting of -H, alkyl, optionally substituted aryl, optionally substituted alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted -alkylaryl, $-C(R^2)_2OC(O)NR^2{}_2$, $-NR^2\text{-}C(O)\text{-}R^3$, $-C(R^2)_2\text{-}\ OC(O)R^3$, $-C(R^2)_2\text{-}O\text{-}C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$, -alkyl-S-C(O)R^3, -alkyl-S-S-alkylhydroxy, and -alkyl-S-S-S-alkylhydroxy,

when Y is $-NR^6-$, then R^1 attached to $-NR^6-$ is independently selected from the group consisting of -H, $-[C(R^2)_2]_q\text{-}COOR^3$, $-C(R^4)_2COOR^3$, $-[C(R^2)_2]_q\text{-}C(O)SR$, and -cycloalkylene-$COOR^3$;

or when either Y is independently selected from -O- and $-NR^6-$, then together R^1 and R^1 are -alkyl-S-S-alkyl- to form a cyclic group, or together R^1 and R^1 are



,

wherein

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, that is fused to an aryl group at the beta and gamma position to the Y attached to the phosphorus;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$aryl, -CH(aryl)OH, $-CH(CH=CR^2_2)OH$, $-CH(C\equiv CR^2)OH$, $-R^2$, $-NR^2_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2$NHaryl, $-(CH_2)_p-OR^2$, and $-(CH_2)_p-SR^2$;

p is an integer 2 or 3;

q is an integer 1 or 2;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-R^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group consisting of -H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^6 is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

n is an integer from 1 to 3;

R^{18} is independently selected from the group consisting of H, lower alkyl, aryl, aralkyl, or together with R^{12} is connected via 1-4 carbon atoms to form a cyclic group;

each R^{12} and R^{13} is independently selected from the group consisting of H, lower alkyl, lower aryl, lower aralkyl, all optionally substituted, or R^{12} and R^{13} together are connected via 2-6 carbon atoms to form a cyclic group;

each R^{14} is independently selected from the group consisting of $-OR^{17}$, $-N(R^{17})_2$, $-NHR^{17}$, and $-SR^{17}$;

R^{15} is selected from the group consisting of -H, lower alkyl, lower aryl, lower arakyl, or together with R^{16} is connected via 2-6 atoms, optionally including 1 heteroatom selected from the group consisting of O, N, and S;

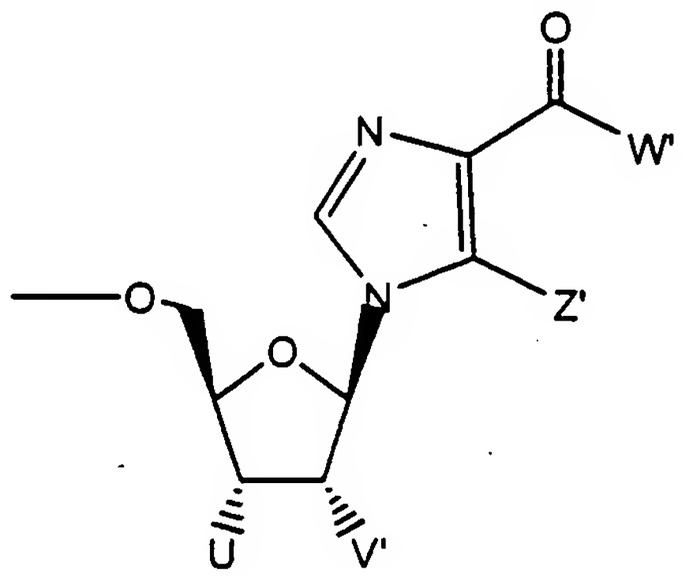
R^{16} is selected from the group consisting of $-(CR^{12}R^{13})_n-C(O)-R^{14}$, lower alkyl, lower aryl, lower aralkyl, or together with R^{15} is connected via 2-6 atoms, optionally including 1 heteroatom selected from the group consisting of O, N, and S;

each R^{17} is independently selected from the group consisting of lower alkyl, lower aryl, and lower aralkyl, or together R^{17} and R^{17} on N is connected via 2-6 atoms, optionally including 1 heteroatom selected from the group consisting of O, N, and S;

with the proviso that when only one Y is –O-, and it is not part of a cyclic group containing the other Y, then the other Y must be $-N(R^{18})-(CR^{12}R^{13})-C(O)-R^{14}$.

and pharmaceutically acceptable prodrugs and salts thereof.

10. The pharmaceutical composition of claim 9 wherein said M is:



wherein

Z' is selected from the group consisting of alkyl or halogen,

U and V' are independently selected from the group consisting of hydrogen, hydroxy, acyloxy or when taken together form a lower cyclic ring containing at least one oxygen;

W' is selected from the group consisting of amino and lower alkyl amino;

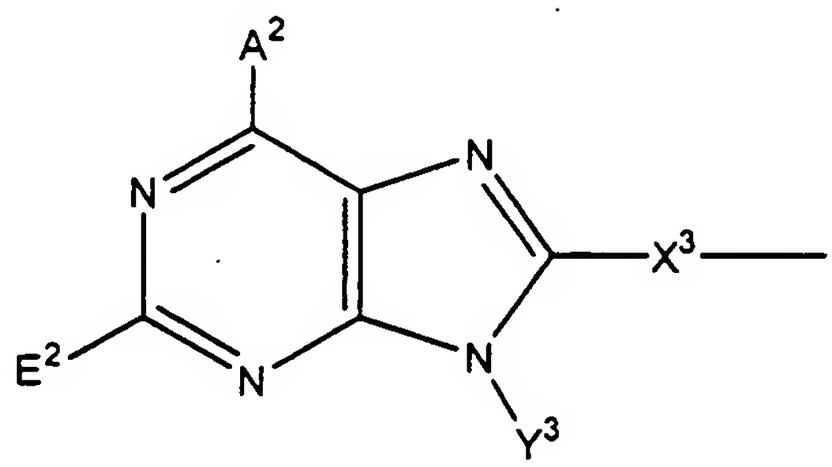
and pharmaceutically acceptable salts thereof.

11. The pharmaceutical composition of claim 10 wherein said insulin sensitizer is a thiazolidinedione.

12. The pharmaceutical composition of claim 10 wherein said insulin sensitizer is a PPAR γ agonist.

13. The pharmaceutical composition of claim 10 wherein said insulin sensitizer is a RXR ligand.

14. The pharmaceutical composition of claim 9 wherein M is:



wherein

A^2 is selected from the group consisting of $-NR^8_2$, $NHSO_2R^3$, $-OR^5$, $-SR^5$, halogen, lower alkyl, $-CON(R^4)_2$, guanidine, amidine, -H, and perhaloalkyl;

E^2 is selected from the group consisting of -H, halogen, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, -CN, and $-NR^7_2$;

X^3 is selected from the group consisting of -alkyl(hydroxy)-, -alkyl-, -alkynyl-, -aryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, -alkyloxy-, -alkylthioalkyl-, -alkylthio-, -alkylaminocarbonyl-, -alkylcarbonylamino-, -alicyclic-, -aralkyl-, -alkylaryl-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and -alkylaminocarbonylamino-, all optionally substituted; with the proviso that X^3 is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

Y^3 is selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H are optionally substituted;

each R^4 is independently selected from the group consisting of –H and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^7 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

R^8 is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidendate alkyl;

R^{10} is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl; and

R^{11} is selected from the group consisting of alkyl, aryl, $-NR^2_2$, and $–OR^2$, and pharmaceutically acceptable prodrugs and salts thereof.

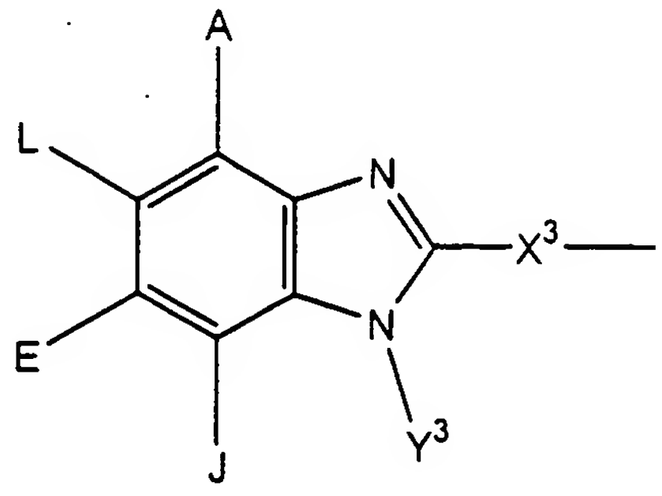
pharmaceutically acceptable prodrugs and salts thereof.

15. The pharmaceutical composition of claim 13 wherein said insulin sensitizer is a thiazolidinedione.

16. The pharmaceutical composition of claim 13 wherein said insulin sensitizer is a PPAR γ agonist.

17. The pharmaceutical composition of claim 13 wherein said insulin sensitizer is a RXR ligand.

18. The pharmaceutical composition of claim 9 wherein M is:



wherein:

A, E, and L are selected from the group consisting of $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidine, amidine, $-NHSO_2R^5$, $-SO_2NR^4_2$, -CN, sulfoxide, perhaloacyl, perhaloalkyl, perhaloalkoxy, C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, and lower alicyclic, or together A and L form a cyclic group, or together L and E form a cyclic group, or together E and J form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

J is selected from the group consisting of $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-C(O)R^{11}$, -CN, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic group including aryl, cyclic alkyl and heterocyclic alkyl;

X^3 is selected from the group consisting of -alkyl(hydroxy)-, -alkyl-, -alkynyl-, -aryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, -alkyloxy-, -alkylthioalkyl-, -alkylthio-, -alkylaminocarbonyl-, -alkylcarbonylamino-, -alicyclic-, -aralkyl-, -alkylaryl-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and -alkylaminocarbonylamino-, all optionally substituted; with the proviso that X^3 is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

Y^3 is selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H are optionally substituted;

R^4 is independently selected from the group consisting of –H and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^7 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

R^8 is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidendate alkyl;

R^{10} is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

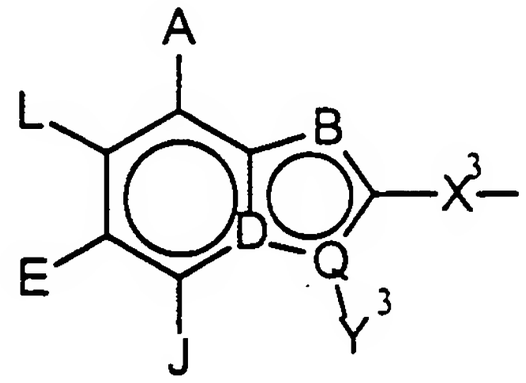
R^{11} is selected from the group consisting of alkyl, aryl, $-NR^2{}_2$, and $-OR^2$, and pharmaceutically acceptable prodrugs and salts thereof.

19. The pharmaceutical composition of claim 18 wherein said insulin sensitizer is a thiazolidinedione.

20. The pharmaceutical composition of claim 18 wherein said insulin sensitizer is a PPAR γ agonist.

21. The pharmaceutical composition of claim 18 wherein said insulin sensitizer is a RXR ligand.

22. The pharmaceutical composition of claim 9 wherein M is:



wherein:

B is selected from the group consisting of -NH-, -N= and -CH=;

D is selected from the group consisting of -C= and -N-;

Q is selected from the group consisting of -C= and -N- with the proviso that when B is -NH- then Q is -C= and D is -C=, when B is -CH= then Q is -N- and D is -C=, when B is -N=, then D is -N- and Q is -C=;

A, E, and L are selected from the group consisting of $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidine, amidine, $-NHSO_2R^5$, $-SO_2NR^4_2$, -CN, sulfoxide, perhaloacyl, perhaloalkyl, perhaloalkoxy, C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, and lower alicyclic, or together A and L form a cyclic group, or together L and E form a cyclic group, or together E and J form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

J is selected from the group consisting of $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-C(O)R^{11}$, -CN, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic group including aryl, cyclic alkyl and heterocyclic alkyl;

X^3 is selected from the group consisting of -alkyl(hydroxy)-, -alkyl-, -alkynyl-, -aryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, -alkyloxy-, -alkylthioalkyl-, -alkylthio-, -alkylaminocarbonyl-, -alkylcarbonylamino-, -alicyclic-, -aralkyl-, -alkylaryl-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and -alkylaminocarbonylamino-, all optionally substituted; with the proviso that X^3 is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

Y^3 is selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H are optionally substituted;

R^4 is independently selected from the group consisting of –H and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^7 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and -C(O)R^{10};

R^8 is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, -C(O)R^{10}, or together they form a bidentate alkyl;

R^{10} is selected from the group consisting of -H, lower alkyl, -NH_2, lower aryl, and lower perhaloalkyl;

R^{11} is selected from the group consisting of alkyl, aryl, -NR^2_2 and -OR^3; and

pharmaceutically acceptable prodrugs and salts thereof.

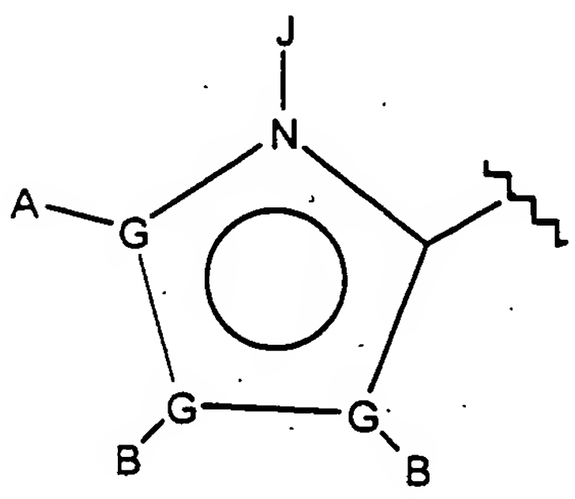
23. The pharmaceutical composition of claim 22 wherein said insulin sensitizer is a thiazolidinedione.

24. The pharmaceutical composition of claim 22 wherein said insulin sensitizer is a PPAR γ agonist.

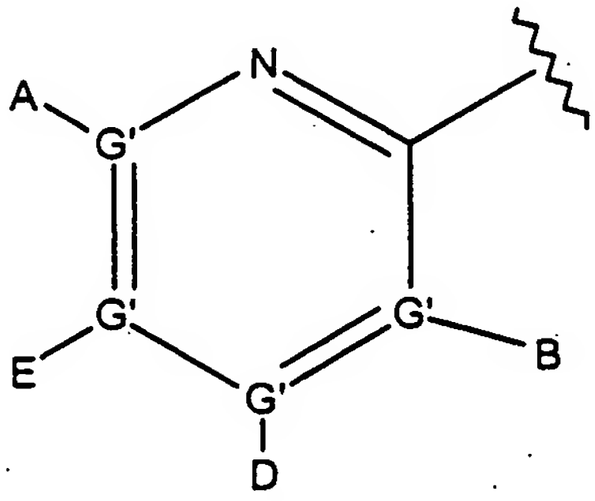
25. The pharmaceutical composition of claim 22 wherein said insulin sensitizer is a RXR ligand.

26. The pharmaceutical composition of claim 9 wherein M is R^5-X-:

wherein R^5 is selected from the group consisting of:



and



wherein:

each G is independently selected from the group consisting of C, N, O, S, and Se, and wherein only one G may be O, S, or Se, and at most one G is N;

each G' is independently selected from the group consisting of C and N and wherein no more than two G' groups are N;

A is selected from the group consisting of -H, $-NR^4_2$, $-CONR^4_2$, $-CO_2R^3$, halo, $-S(O)R^3$, $-SO_2R^3$, alkyl, alkenyl, alkynyl, perhaloalkyl, haloalkyl, aryl, $-CH_2OH$, $-CH_2NR^4_2$, $-CH_2CN$, -CN, $-C(S)NH_2$, $-OR^3$, $-SR^3$, $-N_3$, $-NHC(S)NR^4_2$, -NHAc, and null;

each B and D are independently selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, alkoxyalkyl, $-C(O)R^{11}$, $-C(O)SR^3$, $-SO_2R^{11}$, $-S(O)R^3$, -CN, $-NR^9_2$, $-OR^3$, $-SR^3$, perhaloalkyl, halo, $-NO_2$, and null, all except -H, -CN, perhaloalkyl, $-NO_2$, and halo are optionally substituted;

E is selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, alkoxyalkyl, $-C(O)OR^3$, $-CONR^4_2$, -CN, $-NR^9_2$, $-NO_2$, $-OR^3$, $-SR^3$, perhaloalkyl, halo, and null, all except -H, -CN, perhaloalkyl, and halo are optionally substituted;

J is selected from the group consisting of -H and null;

X is an optionally substituted linking group that links R^5 to the phosphorus atom via 2-4 atoms, including 0-1 heteroatoms selected from N, O, and S, except that if X is urea or carbamate there is 2 heteroatoms, measured by the shortest path between R^5 and the phosphorus atom, and wherein the atom attached to the phosphorus is a carbon atom, and wherein X is selected from the group consisting of -alkyl(hydroxy)-, -alkynyl-, -heteroaryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, -alkyloxy-, -alkylthioalkyl-, -alkylthio-, -alkylaminocarbonyl-, -alkylcarbonylamino-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and -alkylaminocarbonylamino-, all optionally substituted; with the proviso that X is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group consisting of -H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

each R^9 is independently selected from the group consisting of -H, alkyl, aralkyl, and alicyclic, or together R^9 and R^9 form a cyclic alkyl group;

R^{11} is selected from the group consisting of alkyl, aryl, $-NR^2_2$, and $-OR^2$;

and with the proviso that:

1) when G' is N, then the respective A, B, D, or E is null;

2) at least one of A and B, or A, B, D, and E is not selected from the group consisting of -H or null;

3) when R^5 is a six-membered ring, then X is not any 2 atom linker, an optionally substituted -alkyloxy-, or an optionally substituted -alkylthio-;

4) when G is N, then the respective A or B is not halogen or a group directly bonded to G via a heteroatom;

5) when X is not a -heteroaryl- group, then R^5 is not substituted with two or more aryl groups;

and pharmaceutically acceptable prodrugs and salts thereof.

27. The compounds of claim 26 wherein when R^5 is 2-thiazolyl, 2-oxazolyl, or 2-selenazolyl, and X is -alkoxyalkyl-, -alkylthioalkyl-, -alkyloxy-, or -alkylthio-, then A is not $-CONH_2$ and B is not -H.

28. The compounds of claim 26 wherein when R^5 is 2-thiazolyl, 2-oxazolyl, or 2-selenazolyl, then X is not -alkyloxyalkyl-, -alkylthioalkyl-, -alkyloxy-, or -alkylthio-.

29. The compounds of claim 27 wherein said compound of formula I or formula IA has an IC_{50} of ≤ 50 μ M on glucose production in isolated rat hepatocytes.

30. The compounds of claim 29 wherein R^5 is selected from the group consisting of pyrrolyl, imidazolyl, oxazolyl, thiazolyl, isothiazolyl, 1,2,4-thiadiazolyl, pyrazolyl, isoxazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, and 1,3-selenazolyl, all of which contain at least one substituent.

31. The compounds of claim 30 wherein R^5 is not 2-thiazolyl, or 2-oxazolyl.

32. The compounds of claim 31 wherein

A is selected from the group consisting of -H, $-NR^4_2$, $-CONR^4_2$, $-CO_2R^3$, halo, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C1-C6 perhaloalkyl, C1-C6 haloalkyl, aryl,

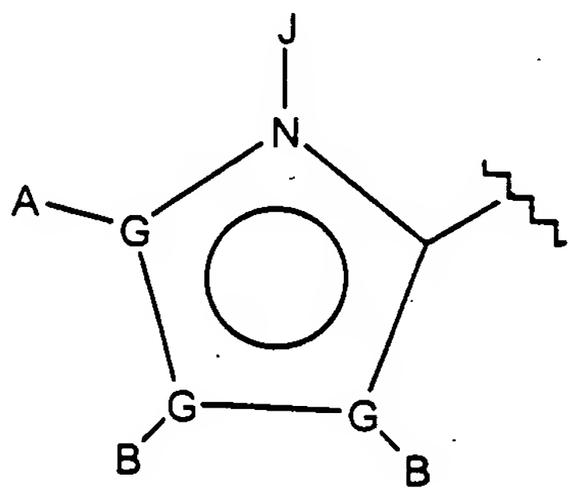
-CH_2OH, -$CH_2NR^4_2$, -CH_2CN, -CN, -$C(S)NH_2$, -OR^4, -SR^4, -N_3, -$NHC(S)NR^4_2$, -NHAc, and null;

each B and D are independently selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, alkoxyalkyl, -$C(O)R^{11}$, -$C(O)SR^3$, -SO_2R^{11}, -$S(O)R^3$, -CN, -NR^2_2, -OR^3, -SR^3, perhaloalkyl, halo, and null, all except -H, -CN, perhaloalkyl, and halo are optionally substituted;

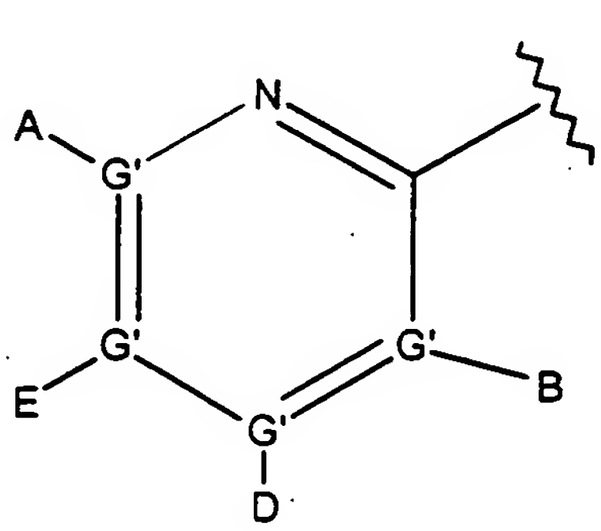
E is selected from the group consisting of -H, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, aryl, C4-C6 alicyclic, alkoxyalkyl, -$C(O)OR^3$, -$CONR^4_2$, -CN, -NR^9_2, -OR^3, -SR^3, C1-C6 perhaloalkyl, halo, and null, all except -H, -CN, perhaloalkyl, and halo are optionally substituted; and

each R^4 is independently selected from the group consisting of -H, and C1-C2 alkyl.

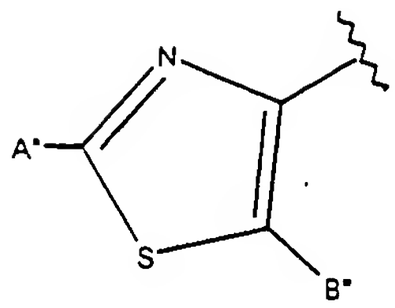
33. The compounds of claim 31 wherein R^5 is:

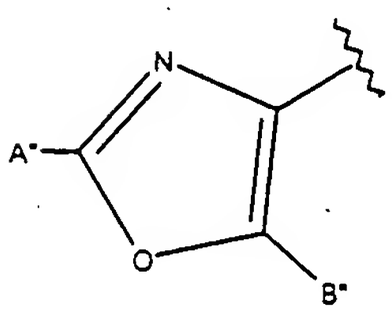


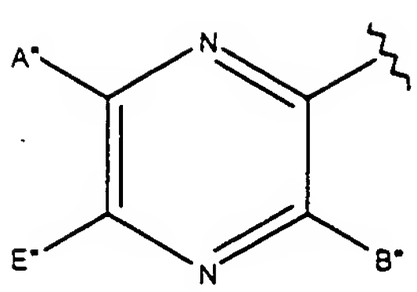
34. The compounds of claim 31 wherein R^5 is:

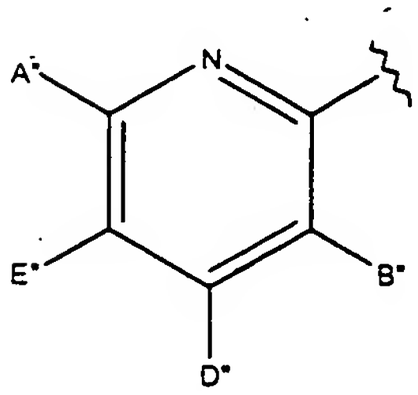


35. The compounds of claim 31 wherein R^5 is selected from the group consisting of:

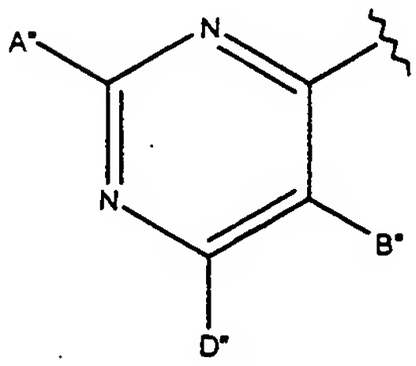








, and



;

wherein

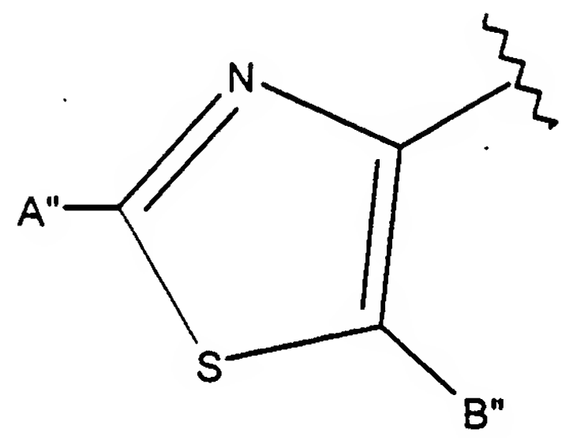
A" is selected from the group consisting of -H, $-NR^4_2$, $-CONR^4_2$, $-CO_2R^3$, halo, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C1-C6 perhaloalkyl, C1-C6 haloalkyl, aryl, $-CH_2OH$, $-CH_2NR^4_2$, $-CH_2CN$, -CN, $-C(S)NH_2$, $-OR^3$, $-SR^3$, $-N_3$, $-NHC(S)NR^4_2$, and -NHAc;

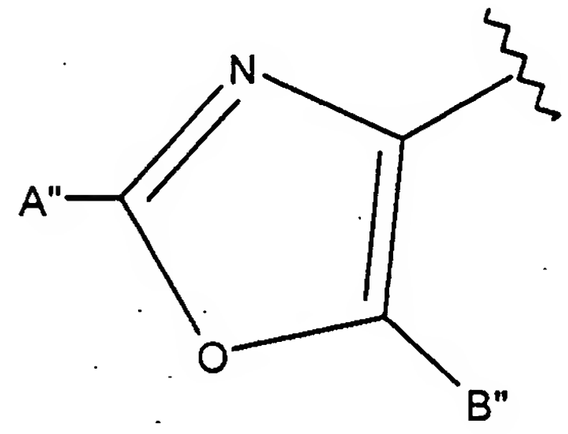
B" and D" are independently selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, alkoxyalkyl, $-C(O)R^{11}$, $-C(O)SR^3$, $-SO_2R^{11}$, $-S(O)R^3$, -CN, $-NR^9_2$, $-OR^3$, $-SR^3$, perhaloalkyl, and halo, all except -H, -CN, perhaloalkyl, and halo are optionally substituted;

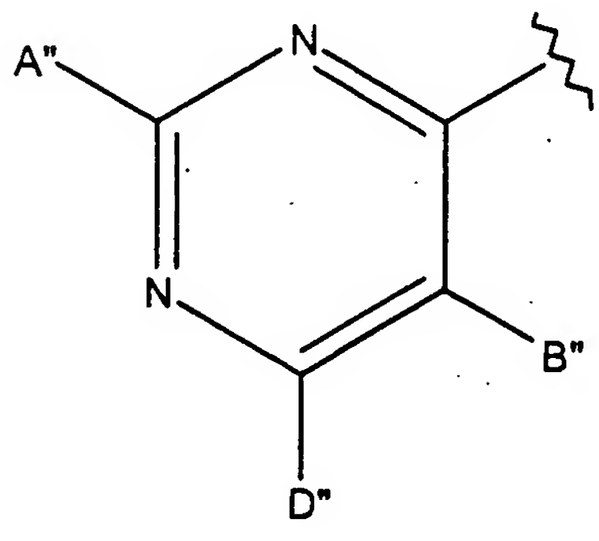
E" is selected from the group consisting of -H, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C4-C6 alicyclic, alkoxyalkyl, $-C(O)OR^3$, $-CONR^4_2$, -CN, $-NR^9_2$, $-OR^3$, $-SR^3$, C1-C6 perhaloalkyl, and halo, all except H, -CN, perhaloalkyl, and halo are optionally substituted; and

each R^4 is independently selected from the group consisting of -H and C1-C2 alkyl.

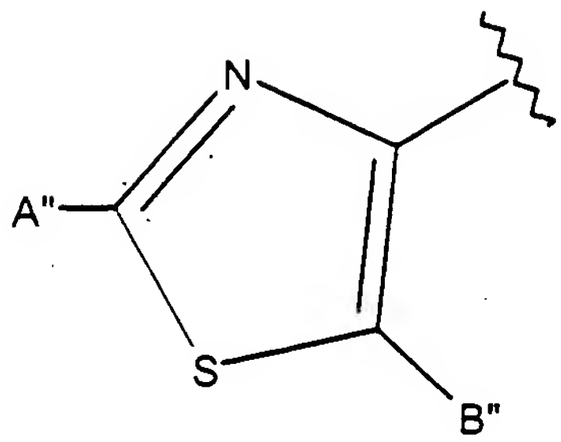
36. The compounds of claim 35 wherein R^5 is selected from the group consisting of:

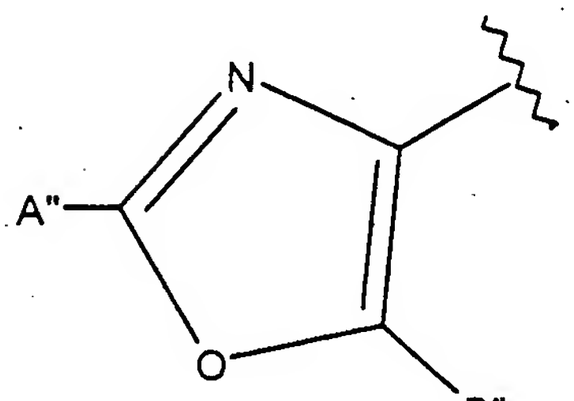




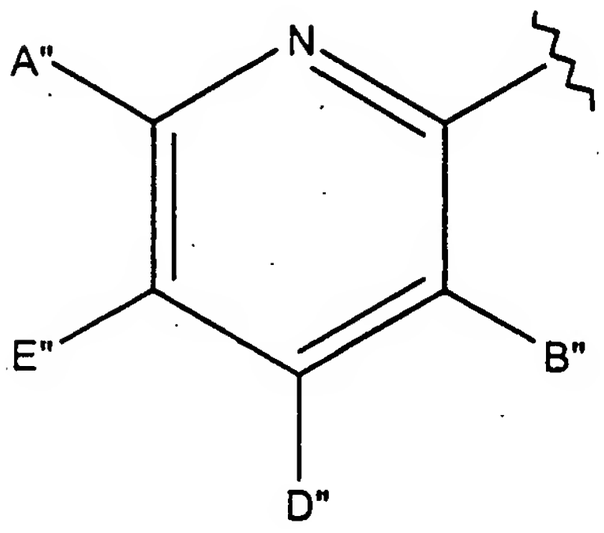


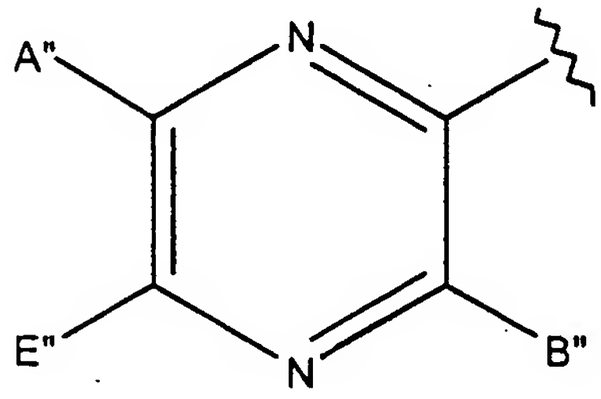
37. The compounds of claim 35 wherein R^5 is selected from the group consisting of:



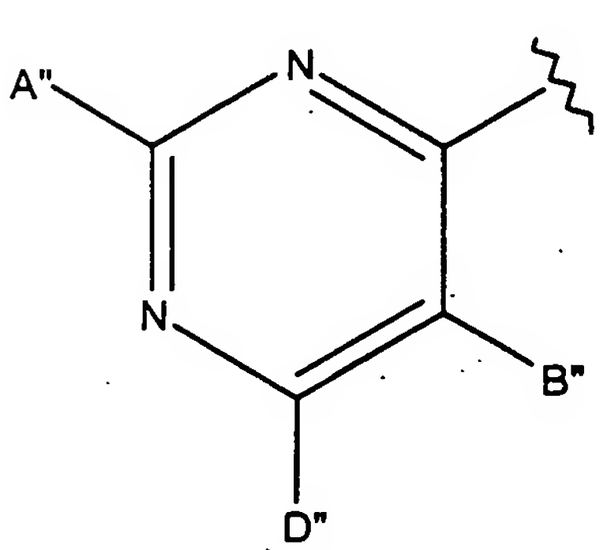


38. The compounds of claim 35 wherein R^5 is selected from the group consisting of:





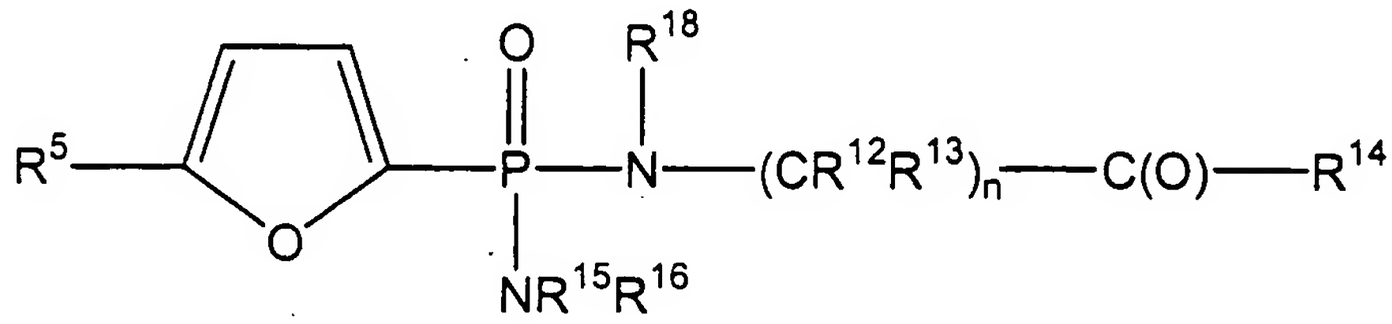
, and



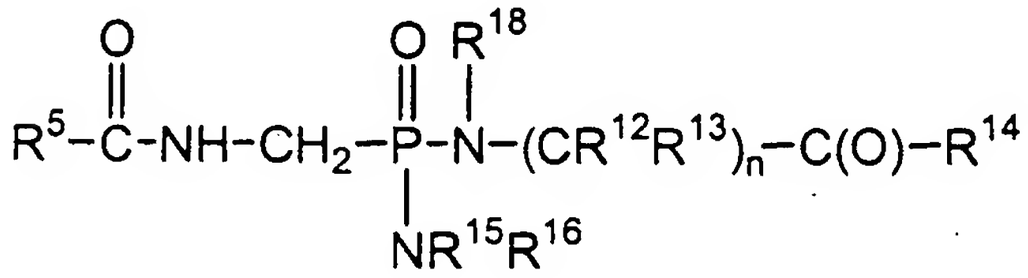
39. The compounds of claim 32 wherein X is selected from the group consisting of -heteroaryl-, -alkylcarbonylamino-, -alkylaminocarbonyl-, and -alkoxycarbonyl-.

40. The compounds of claim 39 wherein X is selected from the group consisting of -heteroaryl-, and -alkoxycarbonyl-.

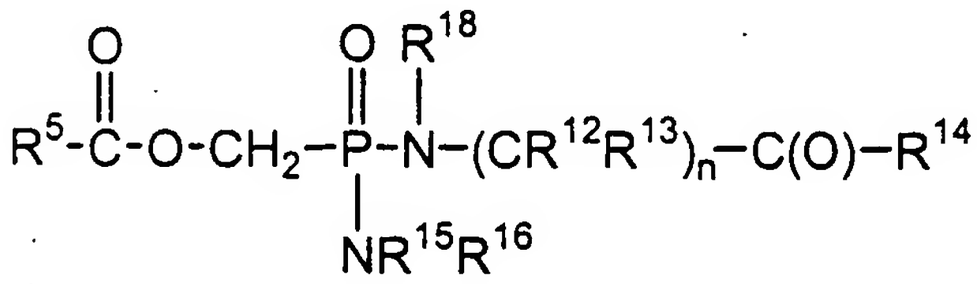
41. The compounds of claim 32 wherein said compound is a compound of formulae VII, VIII, or IX:



(VII)



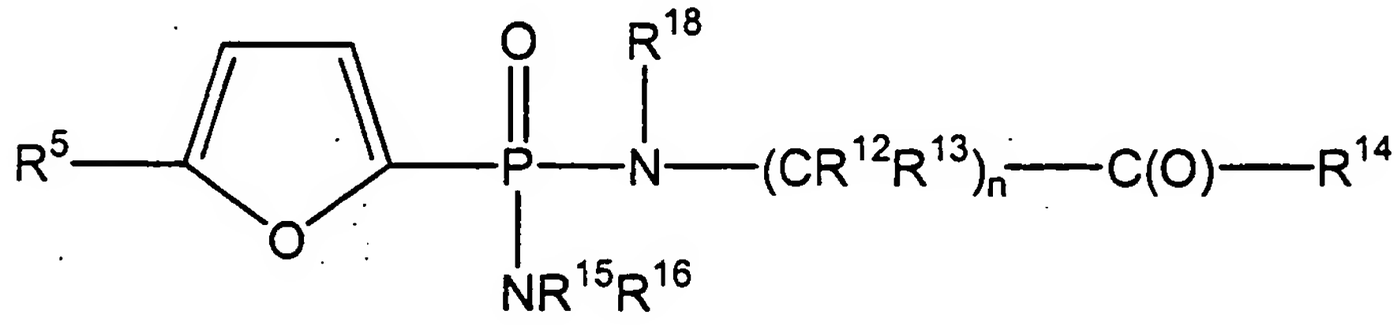
, and (VIII)



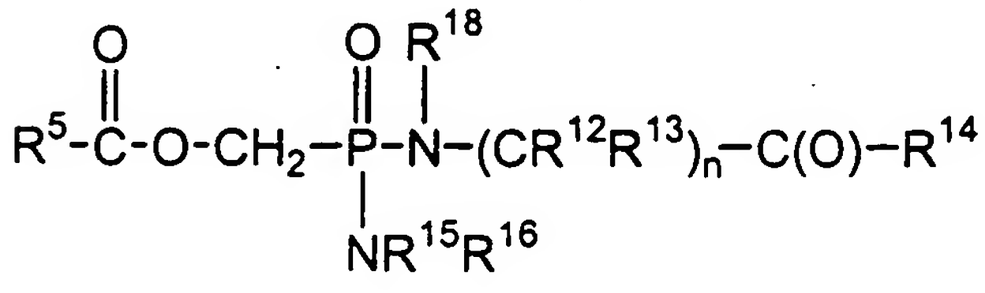
(IX)

42. The compounds of claim 35 wherein X is selected from the group consisting of -heteroaryl-, -alkylcarbonylamino-, -alkylaminocarbonyl-, and -alkoxycarbonyl-.

43. The compounds of claim 41 wherein said compound is a compound of formulae VII or IX:



(VII)



(IX)

44. The compounds of claim 42 wherein A" is selected from the group consisting of $-NH_2$, $-CONH_2$, halo, $-CH_3$, $-CF_3$, $-CH_2$-halo, -CN, $-OCH_3$, $-SCH_3$, and -H.

45. The compounds of claim 44 wherein A" is selected from the group consisting of $-NH_2$, -Cl, -Br, and $-CH_3$.

46. The compounds of claim 42 wherein each B" is selected from the group consisting of -H, $-C(O)R^{11}$, $-C(O)SR^3$, alkyl, aryl, alicyclic, halo, -CN, $-SR^3$, $-NR^9_2$, and $-OR^3$.

47. The compounds of claim 46 wherein each B" is selected from the group consisting of -H, $-C(O)OR^3$, $-C(O)SR^3$, C1-C6 alkyl, alicyclic, halo, heteroaryl, and $-SR^3$.

48. The compounds of claim 42 wherein D" is selected from the group consisting of -H, $-C(O)R^{11}$, $-C(O)SR^3$, alkyl, aryl, alicyclic, halo, $-NR^9_2$, and $-SR^3$.

49. The compounds of claim 48 wherein D" is selected from the group consisting of -H, $-C(O)OR^3$, lower alkyl, alicyclic, and halo.

50. The compounds of claim 42 wherein E" is selected from the group consisting of -H, C1-C6 alkyl, lower alicyclic, halogen, -CN, $-C(O)OR^3$, $-SR^3$, and $-CONR^4_2$.

51. The compounds of claim 50 wherein E" is selected from the group consisting of -H, -Br, and -Cl.

52. The compounds of claim 31 wherein R^{18} is selected from the group consisting of -H, methyl, and ethyl.

53. The compounds of claim 52 wherein R^{18} is selected from the group consisting of -H and methyl.

54. The compounds of claim 53 wherein R^{18} is -H.

55. The compounds of claim 31 wherein each R^{12} and R^{13} is independently selected from the group consisting of -H, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, $-CH_2CH_2-SCH_3$, phenyl, and benzyl, or together R^{12} and R^{13} are connected via 2-5 carbon atoms to form a cycloalkyl group.

56. The compounds of claim 55 wherein each R^{12} and R^{13} is independently selected from the group consisting of -H, methyl, i-propyl, i-butyl, and benzyl, or together R^{12} and R^{13} are connected via 2-5 carbon atoms to form a cycloalkyl group.

57. The compounds of claim 56 wherein each R^{12} and R^{13} is independently selected from the group consisting of -H, methyl, i-propyl, and benzyl, or together R^{12} and R^{13} are connected via 4 carbon atoms to form a cyclopentyl group.

58. The compounds of claim 57 wherein R^{12} and R^{13} are both -H, both methyl, or R^{12} is H and R^{13} is selected from the group consisting of methyl, i-propyl, and benzyl.

59. The compounds of claim 58 wherein n is 1, and R^{12} is –H, then the carbon attached to R^{12} and R^{13} has S stereochemistry.

60. The compounds of claim 31 wherein n is an integer of from 1-2.

61. The compounds of claim 60 wherein n is 1.

62. The compounds of claim 31 wherein each R^{14} is independently selected from the group consisting of $-OR^{17}$, and $-SR^{17}$; and R^{17} is selected from the group consisting of optionally substituted methyl, ethyl, propyl, t-butyl, and benzyl.

63. The compounds of claim 62 wherein each R^{14} is independently selected from the group consisting of $-OR^{17}$; and R^{17} is selected from the group consisting of methyl, ethyl, propyl, and benzyl.

64. The compounds of claim 63 wherein R^{17} is selected from the group consisting of ethyl, and benzyl.

65. The compounds of claim 31 wherein R^{15} is not H.

66. The compounds of claim 65 wherein R^{15} and R^{16} are independently selected from the group consisting of lower alkyl, and lower aralkyl, or together R^{15} and R^{16} are connected via 2-6 atoms, optionally including 1 heteroatom selected from the group consisting of O, N, and S.

67. The compounds of claim 66 wherein R^{15} and R^{16} are independently selected from the group consisting of C1-C6 alkyl, or together R^{15} and R^{16} are connected via 2-6 atoms, optionally including 1 heteroatom selected from the group consisting of O, N, and S.

68. The compounds of claim 67 wherein $-NR^{15}R^{16}$ is a cyclic amine.

69. The compounds of claim 68 wherein $-NR^{15}R^{16}$ is selected from the group consisting of morpholinyl and pyrrolidinyl.

70. The compounds of claim 31 wherein R^{16} is $-(CR^{12}R^{13})_n-C(O)-R^{14}$.

71. The compounds of claim 61 wherein

R^{18} is selected from the group consisting of -H, methyl, and ethyl;

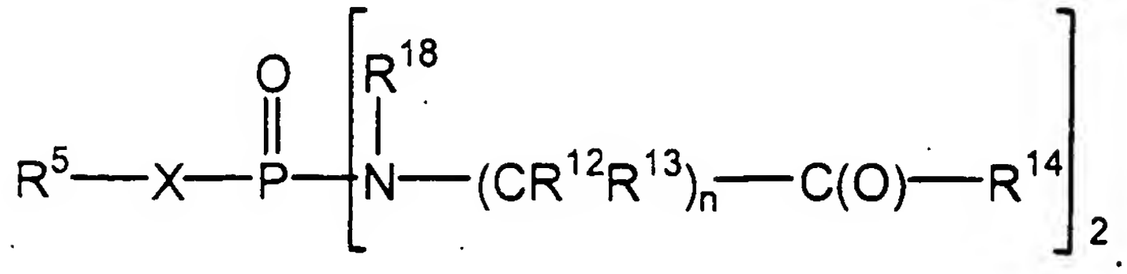
R^{12} and R^{13} are independently selected from the group consisting of -H, methyl, i-propyl, i-butyl, and benzyl, or together are connected via 2-5 carbon atoms to form a cycloalkyl group;

R^{14} is $-OR^{17}$;

R^{17} is selected from the group consisting of methyl, ethyl, propyl, t-butyl, and benzyl; and

R^{15} and R^{16} are independently selected from the group consisting of lower alkyl, and lower aralkyl, or together R^{15} and R^{16} are connected via 2-6 atoms, optionally including 1 heteroatom selected from the group consisting of O, and N.

72. The compounds of claim 70 that are of the formula:



73. The compounds of claim 72 wherein n is 1.

74. The compounds of claim 73 wherein when R^{12} R^{13} are not the same, then H_2N-$CR^{12}R^{13}$-C(O)-R^{14} is an ester, or thioester of a naturally occurring amino acid; and R^{14} is selected from the group consisting of -OR^{17} and 'SR^{17}.

75. The compounds of claim 35 wherein

A" is selected from the group consisting of -NH_2, -$CONH_2$, halo, -CH_3, -CF_3, -CH_2-halo, -CN, -OCH_3, -SCH_3, and -H;

B" is selected from the group consisting of -H, -C(O)R^{11}, -C(O)SR^3, alkyl, aryl, alicyclic, halo, -CN, -SR^3, OR^3 and -$NR^9{}_2$;

D" is selected from the group consisting of -H, -C(O)R^{11}, -C(O)SR^3, -$NR^9{}_2$, alkyl, aryl, alicyclic, halo, and -SR^3;

E" is selected from the group consisting of -H, C1-C6 alkyl, lower alicyclic, halo, -CN, -C(O)OR^3, and -SR^3.

X is selected from the group consisting of -heteroaryl-, -alkoxycarbonyl-, and -alkylaminocarbonyl-, all optionally substituted;

R^{18} and R^{15} are selected from the group consisting of H, and methyl;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

each R^{12} and R^{13} is independently selected from the group consisting of -H, methyl, i-propyl, i-butyl, and benzyl, or together R^{12} and R^{13} are connected via 2-5 carbon atoms to form a cycloalkyl group;

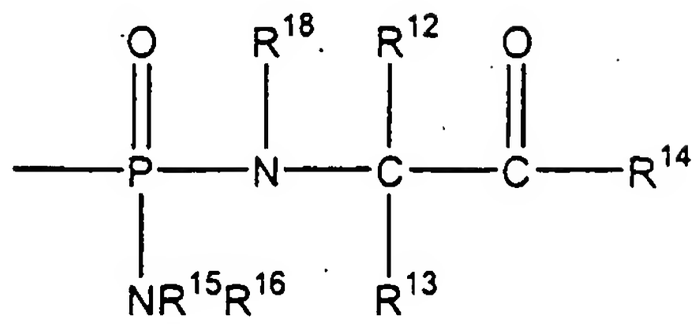
n is 1;

R^{14} is -OR^{17};

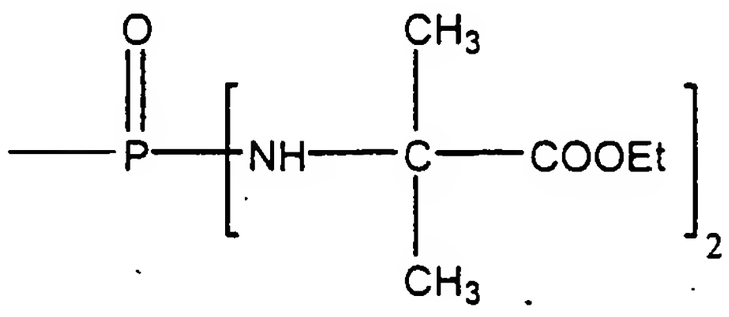
R^{16} is -$(CR^{12}R^{13})_n$-C(O)-R^{14}; and

R^{17} is selected from the group consisting of methyl, ethyl, propyl, phenyl, and benzyl.

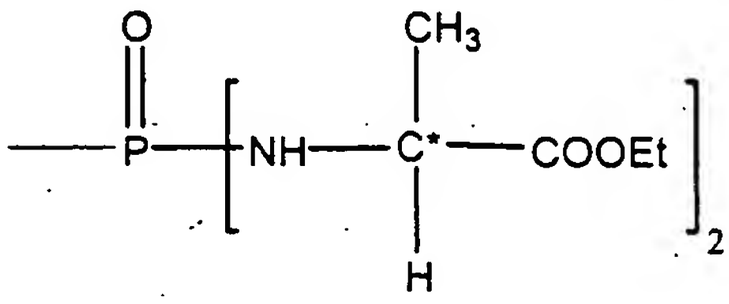
76. The compounds of claim 75 wherein



is selected from the group consisting of

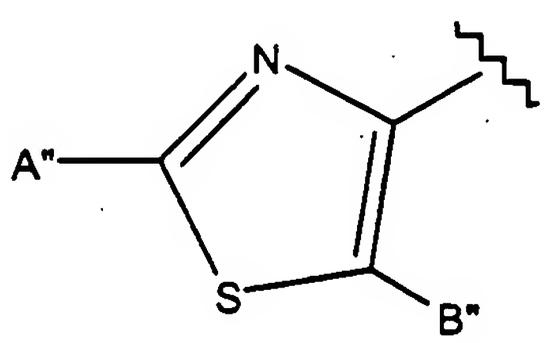


and



wherein C* has S stereochemistry.

77. The compounds of claim 75 wherein R^5 is



X is selected from the group consisting of methylenoxycarbonyl, and furan-2,5-diyl, and pharmaceutically acceptable salts thereof.

78. The compounds of claim 77 wherein A" is $-NH_2$, X is furan-2,5-diyl, and B" is $-S(CH_2)_2CH_3$.

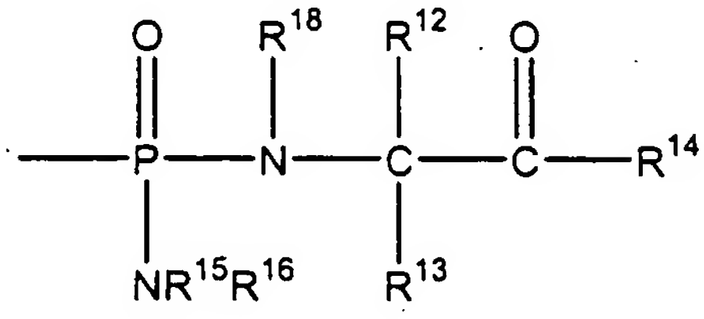
79. The compounds of claim 77 wherein A" is $-NH_2$, X is furan-2,5-diyl, and B" is $-CH_2-CH(CH_3)_2$.

80. The compounds of claim 77 wherein A" is $-NH_2$, X is furan-2,5-diyl, and B" is -COOEt.

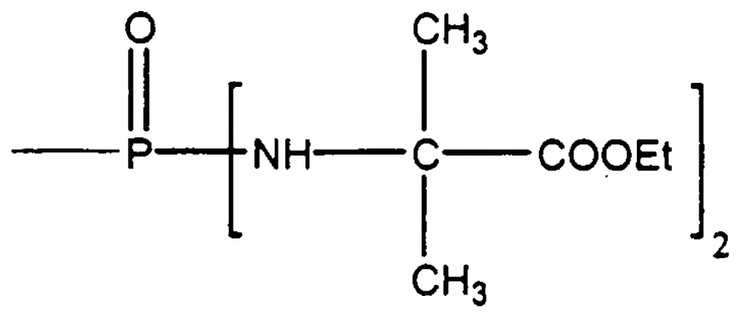
81. The compounds of claim 77 wherein A" is $-NH_2$, X is furan-2,5-diyl, and B" is -SMe.

82. The compounds of claim 77 wherein A" is $-NH_2$, X is methyleneoxycarbonyl, and B" is $-CH(CH_3)_2$.

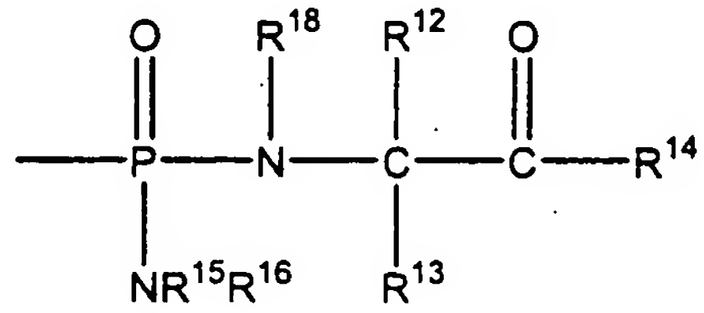
83. The compounds of claim 78 wherein



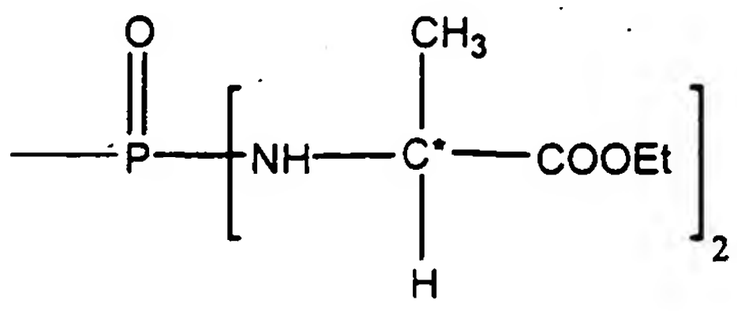
is



84. The compounds of claim 78 wherein

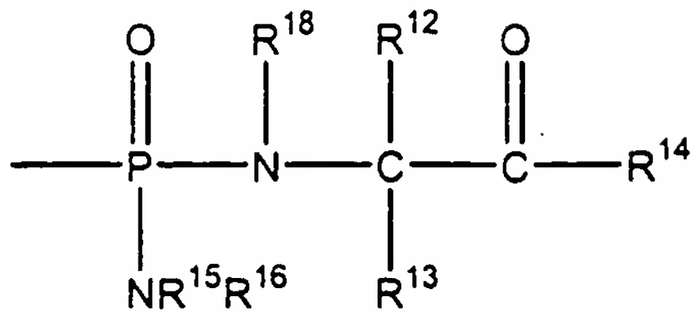


is

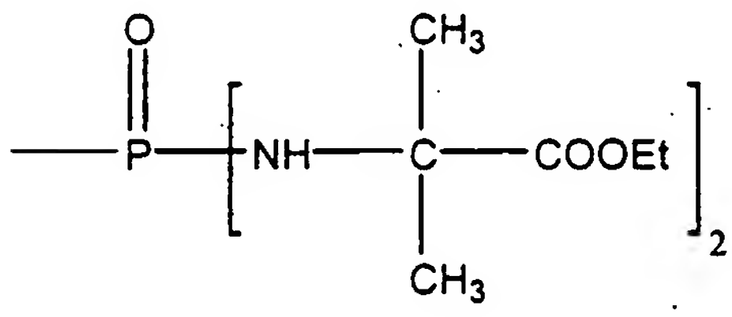


wherein C* has S stereochemistry.

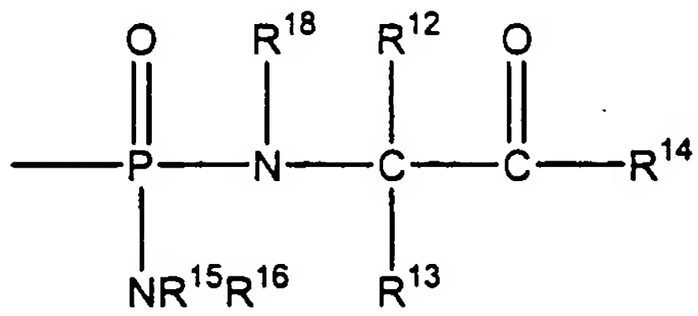
85. The compounds of claim 78 wherein



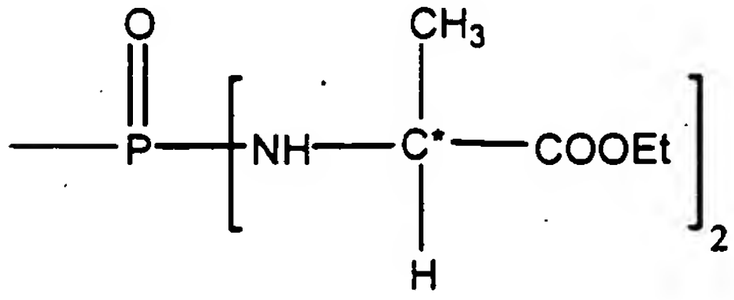
is



86. The compounds of claim 78 wherein

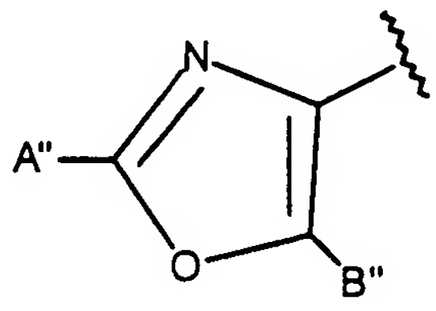


is



wherein C* has S stereochemistry.

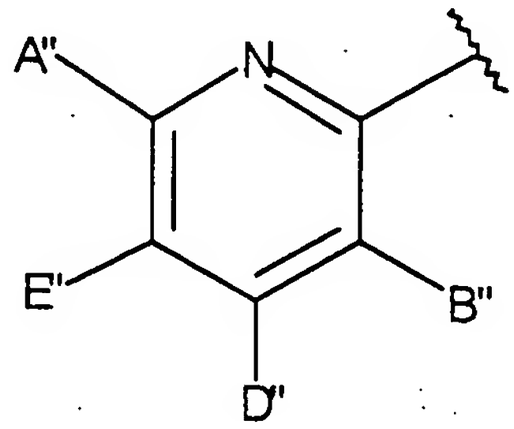
87. The compounds of claim 75 wherein R^5 is



X is selected from the group consisting of furan-2,5-diyl, and methyleneoxycarbonyl, A" is $-NH_2$, and pharmaceutically acceptable salts thereof.

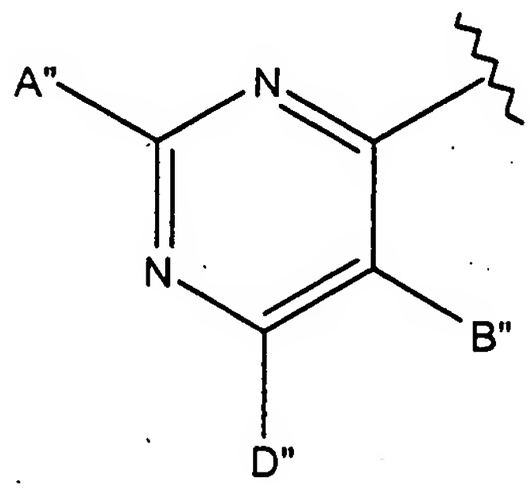
88. The compounds of claim 87 wherein X is furan-2,5-diyl, and B" is $-SCH_2CH_2CH_3$.

89. The compounds of claim 75 wherein R^5 is



A" is $-NH_2$, E" and D" are -H, B" is selected from the group consisting of cyclopropyl, and n-propyl, X is selected from the group consisting of methyleneoxycarbonyl, and furan-2,5-diyl, and pharmaceutically acceptable salts thereof.

90. The compounds of claim 75 wherein R^5 is



A" is $-NH_2$, D" is -H, B" is selected from the group consisting of n-propyl, and cyclopropyl, X is selected from the group consisting of furan-2,5-diyl, and methyleneoxycarbonyl, and pharmaceutically acceptable salts thereof.

91. The pharmaceutical composition of claim 26 wherein said insulin sensitizer is a thiazolidinedione.

92. The pharmaceutical composition of claim 26 wherein said insulin sensitizer is a PPAR γ agonist.

93. The pharmaceutical composition of claim 26 wherein said insulin sensitizer is a RXR ligand.

94. The pharmaceutical composition of claim 1 wherein said combination is administered orally.

95. A method of treating a mammal having diabetes comprising the administration to said mammal a pharmaceutically effective amount of an insulin sensitizer agent and a pharmaceutically effective amount of an FBPase inhibitor or prodrug or salt thereof.

96. The method of claim 95 wherein said insulin sensitizer is a thiazolidinedione.

97. The method of claim 96 wherein said thiazolidinedione is selected from the group consisting of BRL 49653, troglitazone, pioglitazone, ciglitazone, WAY-120,744, englitazone, AD 5075, GI-262570, SB219994, SB219993, and darglitazone.

98. The method of claim 95 wherein said insulin sensitizer is a PPAR γ agonist.

99. The method of claim 98 wherein said PPAR γ agonist is selected from the group consisting of BRL 49653, troglitazone, pioglitazone, ciglitazone, WAY-120,744, englitazone, AD 5075, darglitazone, GI-262570, SB 217092, SB 236636, SB 217092, SB 219994 and SB 219993.

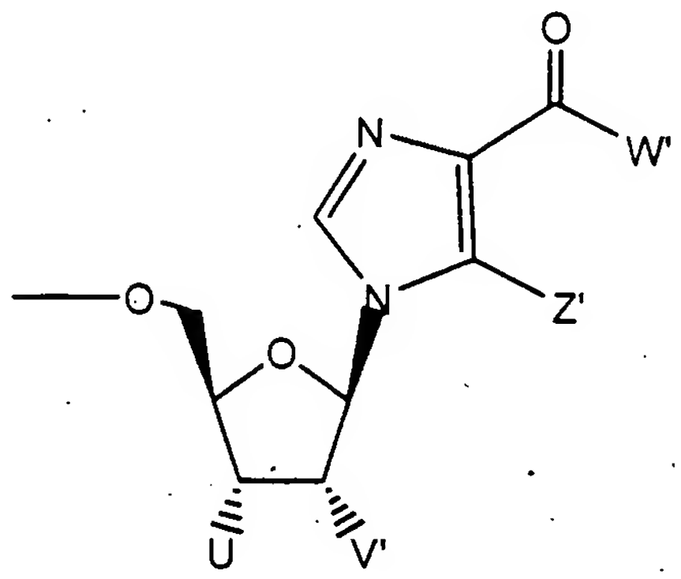
100. The method of claim 95 wherein said insulin sensitizer is a RXR ligand.

101. The method of claim 100 wherein said RXR ligand is selected from the group consisting of 9-cis retinoic acid, LG 100268 and LG 1069.

102. The method of claim 95 wherein said insulin sensitizer is selected from the group consisting of an angiotensin converting enzyme inhibitor, a renin inhibitor, and an angiotensin antagonist.

103. The method of claim 95 wherein said FBPase inhibitor is a compound of claim 9.

104. The method of claim 103 wherein M is:



wherein

Z' is selected from the group consisting of alkyl or halogen,

U and V' are independently selected from the group consisting of hydrogen, hydroxy, acyloxy or when taken together form a lower cyclic ring containing at least one oxygen;

W' is selected from the group consisting of amino and lower alkyl amino;

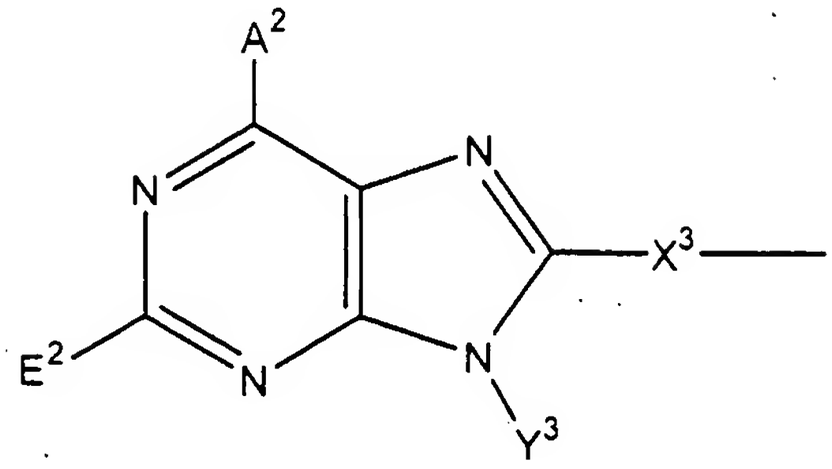
and pharmaceutically acceptable salts thereof.

105. The method of claim 104 wherein said insulin sensitizer is a thiazolidinedione.

106. The method of claim 104 wherein said insulin sensitizer is a PPAR γ agonist.

107. The method of claim 104 wherein said insulin sensitizer is a RXR ligand.

108. The method of claim 103 wherein M is:



wherein

A^2 is selected from the group consisting of $-NR^8_2$, $NHSO_2R^3$, $-OR^5$, $-SR^5$, halogen, lower alkyl, $-CON(R^4)_2$, guanidine, amidine, -H, and perhaloalkyl;

E^2 is selected from the group consisting of -H, halogen, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, -CN, and $-NR^7_2$;

X^3 is selected from the group consisting of -alkyl(hydroxy)-, -alkyl-, -alkynyl-, -aryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, -alkyloxy-, -alkylthioalkyl-, -alkylthio-, -alkylaminocarbonyl-, -alkylcarbonylamino-, -alicyclic-, -aralkyl-, -alkylaryl-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and -alkylaminocarbonylamino-, all optionally substituted; with the proviso that X^3 is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

Y^3 is selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H are optionally substituted;

each R^4 is independently selected from the group consisting of -H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^7 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

R^8 is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidendate alkyl;

R^{10} is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

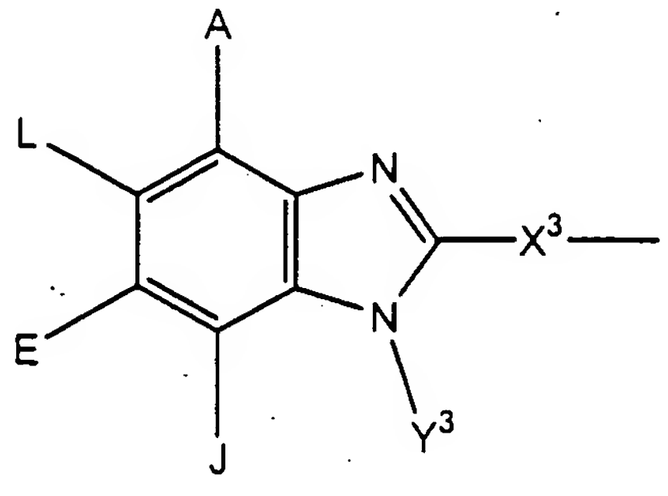
R^{11} is selected from the group consisting of alkyl, aryl, $-NR^2_2$, and $-OR^2$, and pharmaceutically acceptable prodrugs and salts thereof.

109. The method of claim 108 wherein said insulin sensitizer is a thiazolidinedione.

110. The method of claim 108 wherein said insulin sensitizer is a PPAR γ agonist.

111. The method of claim 108 wherein said insulin sensitizer is a RXR ligand.

112. The method of claim 103 wherein M is:



wherein:

A, E, and L are selected from the group consisting of $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidine, amidine, $-NHSO_2R^5$, $-SO_2NR^4_2$, -CN, sulfoxide, perhaloacyl, perhaloalkyl, perhaloalkoxy, C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, and lower alicyclic, or together A and L form a cyclic group, or together L and E form a cyclic group, or together E and J form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

J is selected from the group consisting of $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-C(O)R^{11}$, -CN, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic group including aryl, cyclic alkyl and heterocyclic alkyl;

X^3 is selected from the group consisting of -alkyl(hydroxy)-, -alkyl-, -alkynyl-, -aryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, -alkyloxy-, -alkylthioalkyl-, -alkylthio-, -alkylaminocarbonyl-, -alkylcarbonylamino-, -alicyclic-, -aralkyl-, -alkylaryl-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and -alkylaminocarbonylamino-, all optionally substituted; with the proviso that X^3 is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

Y^3 is selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H are optionally substituted;

each R^4 is independently selected from the group consisting of -H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^7 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

R^8 is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidendate alkyl;

R^{10} is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

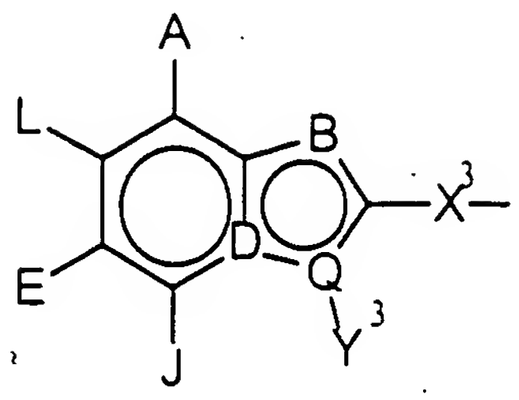
R^{11} is selected from the group consisting of alkyl, aryl, $-NR^2_2$, and $-OR^2$, and pharmaceutically acceptable prodrugs and salts thereof.

113. The method of claim 112 wherein said insulin sensitizer is a thiazolidinedione.

114. The method of claim 112 wherein said insulin sensitizer is a PPAR γ agonist.

115. The method of claim 112 wherein said insulin sensitizer is a RXR ligand.

116. The method of claim 103 wherein M is:



wherein:

B is selected from the group consisting of -NH-, -N= and -CH=;

D is selected from the group consisting of -C= and -N-;

Q is selected from the group consisting of -C= and -N- with the proviso that when B is -NH- then Q is -C= and D is -C=, when B is -CH= then Q is -N- and D is -C=, when B is -N=, then D is -N- and Q is -C=;

A, E, and L are selected from the group consisting of $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidine, amidine, $-NHSO_2R^5$, $-SO_2NR^4_2$, -CN, sulfoxide, perhaloacyl, perhaloalkyl, perhaloalkoxy, C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, and lower alicyclic, or together A and L form a cyclic group, or together L and E form a cyclic group, or together E and J form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

J is selected from the group consisting of $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-C(O)R^{11}$, -CN, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic group including aryl, cyclic alkyl and heterocyclic alkyl;

X^3 is selected from the group consisting of -alkyl(hydroxy)-, -alkyl-, -alkynyl-, -aryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, -alkyloxy-, -alkylthioalkyl-, -alkylthio-, -alkylaminocarbonyl-, -alkylcarbonylamino-, -alicyclic-, -aralkyl-, -alkylaryl-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and

-alkylaminocarbonylamino-, all optionally substituted; with the proviso that X^3 is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

Y^3 is selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H are optionally substituted;

each R^4 is independently selected from the group consisting of -H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^7 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

R^8 is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidentate alkyl;

R^{10} is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

R^{11} is selected from the group consisting of alkyl, aryl, $-NR^2_2$ and $-OR^2$; and

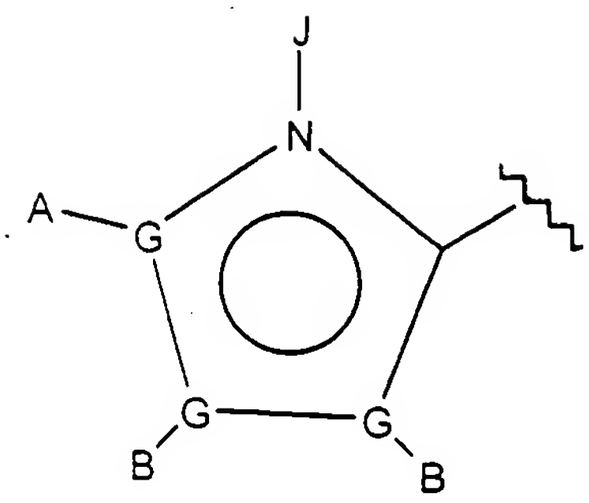
pharmaceutically acceptable prodrugs and salts thereof.

117. The method of claim 116 wherein said insulin sensitizer is a thiazolidinedione.

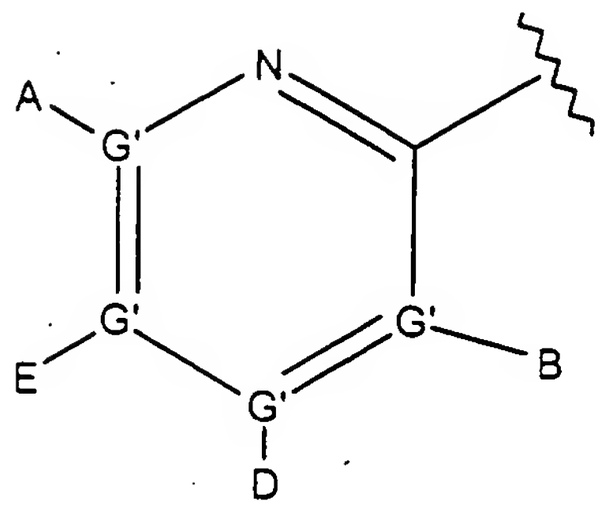
118. The method of claim 116 wherein said insulin sensitizer is a PPAR γ agonist.

119. The method of claim 116 wherein said insulin sensitizer is a RXR ligand.

120. The method of claim 103 wherein M is R^5 -X- wherein R^5 is selected from the group consisting of:



and



wherein:

each G is independently selected from the group consisting of C, N, O, S, and Se, and wherein only one G may be O, S, or Se, and at most one G is N;

each G' is independently selected from the group consisting of C and N and wherein no more than two G' groups are N;

A is selected from the group consisting of -H, $-NR^4_2$, $-CONR^4_2$, $-CO_2R^3$, halo, $-S(O)R^3$, $-SO_2R^3$, alkyl, alkenyl, alkynyl, perhaloalkyl, haloalkyl, aryl, $-CH_2OH$, $-CH_2NR^4_2$, $-CH_2CN$, -CN, $-C(S)NH_2$, $-OR^3$, $-SR^3$, $-N_3$, $-NHC(S)NR^4_2$, -NHAc, and null;

each B and D are independently selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, alkoxyalkyl, $-C(O)R^{11}$, $-C(O)SR^3$, $-SO_2R^{11}$, $-S(O)R^3$, -CN, $-NR^9_2$, $-OR^3$, $-SR^3$, perhaloalkyl, halo, $-NO_2$, and null, all except -H, -CN, perhaloalkyl, $-NO_2$, and halo are optionally substituted;

E is selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, alkoxyalkyl, $-C(O)OR^3$, $-CONR^4_2$, -CN, $-NR^9_2$, $-NO_2$, $-OR^3$, $-SR^3$, perhaloalkyl, halo, and null, all except -H, -CN, perhaloalkyl, and halo are optionally substituted;

J is selected from the group consisting of -H and null;

X is an optionally substituted linking group that links R^5 to the phosphorus atom via 2-4 atoms, including 0-1 heteroatoms selected from N, O, and S, except that if X is urea or carbamate there is 2 heteroatoms, measured by the shortest path between R^5 and the phosphorus atom, and wherein the atom attached to the phosphorus is a carbon atom, and wherein X is selected from the group consisting of -alkyl(hydroxy)-, -alkynyl-, -heteroaryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, -alkyloxy-, -alkylthioalkyl-, -alkylthio-, -alkylaminocarbonyl-, -alkylcarbonylamino-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and -alkylaminocarbonylamino-, all

optionally substituted; with the proviso that X is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2{}_2$;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group consisting of -H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

each R^9 is independently selected from the group consisting of -H, alkyl, aralkyl, and alicyclic, or together R^9 and R^9 form a cyclic alkyl group;

R^{11} is selected from the group consisting of alkyl, aryl, $-NR^2{}_2$, and $-OR^2$;

and with the proviso that:

1) when G' is N, then the respective A, B, D, or E is null;

2) at least one of A and B, or A, B, D, and E is not selected from the group consisting of -H or null;

3) when R^5 is a six-membered ring, then X is not any 2 atom linker, an optionally substituted -alkyloxy-, or an optionally substituted -alkylthio-;

4) when G is N, then the respective A or B is not halogen or a group directly bonded to G via a heteroatom;

5) when X is not a -heteroaryl- group, then R^5 is not substituted with two or more aryl groups;

and pharmaceutically acceptable prodrugs and salts thereof.

121. The method of claim 120 wherein said insulin sensitizer is a thiazolidinedione.

122. The method of claim 120 wherein said insulin sensitizer is a PPAR γ agonist.

123. The method of claim 120 wherein said insulin sensitizer is a RXR ligand.

124. The method of claim 95 wherein said combination is administered orally.

125. The method of claim 98 wherein said combination is administered separately during the day.

126. The method of claim 98 wherein said combination is administered simultaneously during the day.

127. A method of treating a mammal having a disease characterized by insulin resistance and/or hyperglycemia comprising the administration to said mammal an effective amount of an insulin sensitizer agent and an FBPase inhibiting amount of an FBPase inhibitor.

128. The method of claim 95 wherein said disease is characterized by insulin resistance.

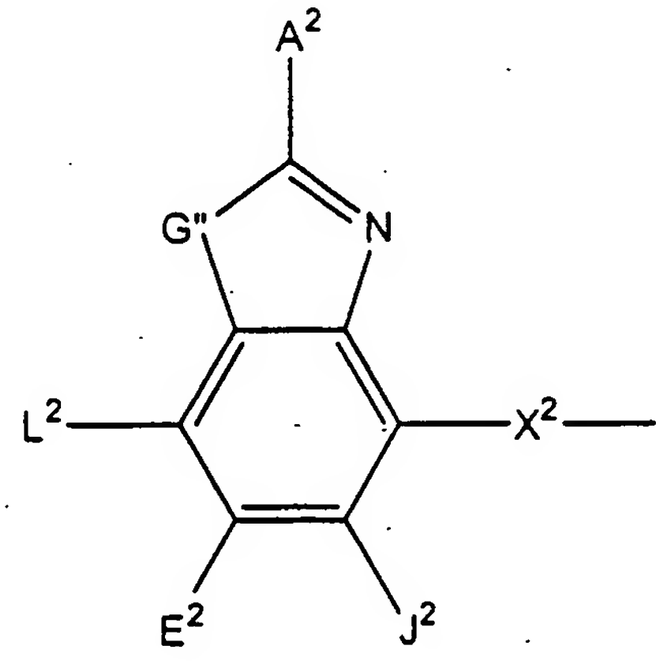
129. The method of claim 95 wherein said disease is characterized by hyperglycemia.

130. The method of claim 95 wherein said disease is obesity.

131. The method of claim 95 wherein said disease is hypertension.

132. The method of claim 95 wherein said disease is polycystic ovarian syndrome.

133. The pharmaceutical composition of claim 9 wherein M is



wherein:

G" is selected from the group consisting of -O- and -S-;

A^2, L^2, E^2, and J^2 are selected from the group consisting of

$-NR^4_2$, $-NO_2$, -H, $-OR^2$, $-SR^2$; $-C(O)NR^4_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidinyl, amidinyl, aryl, aralkyl, alkyoxyalkyl, -SCN, $-NHSO_2R^9$, $-SO_2NR^4_2$, -CN, $-S(O)R^3$, perhaloacyl, perhaloalkyl, perhaloalkoxy, C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, and lower alicyclic, or together L^2 and E^2 or E^2 and J^2 form an annulated cyclic group;

X^2 is selected from the group consisting of $-CR^2_2$-, $-CF_2$-, $-OCR^2_2$-, $-SCR^2_2$-, -O-C(O)-, -S-C(O)-, -O-C(S)-, and $-NR^{19}CR^2_2$-, and wherein in the atom attached to the phosphorus is a carbon atom; with the proviso that X^2 is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group consisting of -H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

each R^9 is independently selected from the group consisting of -H, alkyl, aralkyl, and alicyclic, or together R^9 and R^9 form a cyclic alkyl group;

R^{11} is selected from the group consisting of alkyl, aryl, $-NR^2_2$, and $-OR^2$;

R^{19} is selected from the group consisting of lower alkyl, -H, and $-COR^2$; and

pharmaceutically acceptable prodrugs and salts thereof.

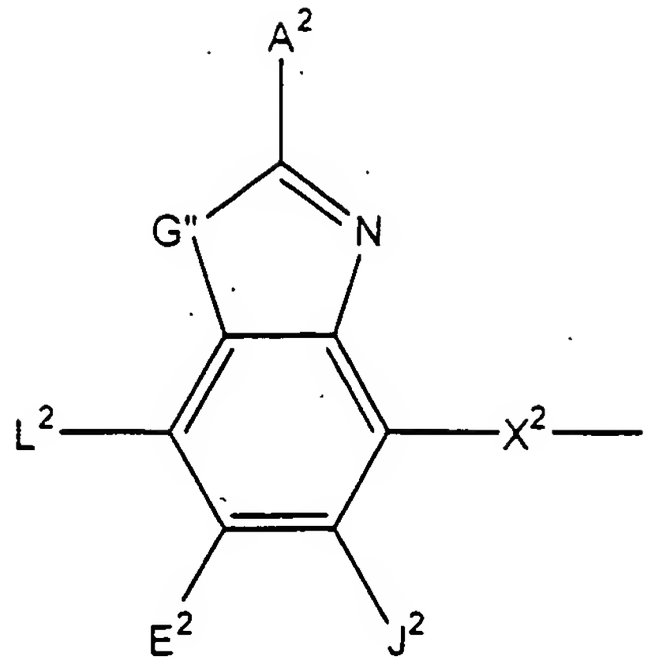
134. The compound of claim 133 wherein G" is -S-.

135. The pharmaceutical composition of claim 134 wherein said insulin sensitizer is a thiazolidinedione.

136. The pharmaceutical composition of claim 134 wherein said insulin sensitizer is a PPAR γ agonist.

137. The pharmaceutical composition of claim 134 wherein said insulin sensitizer is a RXR ligand.

138. The method of claim 103 wherein M is:



wherein:

G" is selected from the group consisting of -O- and -S-;

A^2, L^2, E^2, and J^2 are selected from the group consisting of $-NR^4_2$, $-NO_2$, -H, $-OR^2$, $-SR^2$, $-C(O)NR^4_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidinyl, amidinyl, aryl, aralkyl, alkyoxyalkyl, -SCN, $-NHSO_2R^9$, $-SO_2NR^4_2$, -CN, $-S(O)R^3$, perhaloacyl, perhaloalkyl, perhaloalkoxy, C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, and lower alicyclic, or together L^2 and E^2 or E^2 and J^2 form an annulated cyclic group;

X^2 is selected from the group consisting of $-CR^2_2$-, $-CF_2$-, $-OCR^2_2$-, $-SCR^2_2$-, -O-C(O)-, -S-C(O)-, -O-C(S)-, and $-NR^{19}CR^2_2$-, and wherein in the atom attached to the phosphorus is a carbon atom; with the proviso that X^2 is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group consisting of -H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

each R^9 is independently selected from the group consisting of -H, alkyl, aralkyl, and alicyclic, or together R^9 and R^9 form a cyclic alkyl group;

R^{11} is selected from the group consisting of alkyl, aryl, $-NR^2_2$, and $-OR^2$;

R^{19} is selected from the group consisting of lower alkyl, -H, and $-COR^2$; and pharmaceutically acceptable prodrugs and salts thereof.

139. The method of claim 138 wherein said insulin sensitizer is a thiazolidinedione.

140. The method of claim 138 wherein said insulin sensitizer is a PPAR γ agonist.

141. The method of claim 138 wherein said insulin sensitizer is a RXR ligand.